REMARKS

The claims have been amended to clarify the subject matter. As previously claimed, it was assumed that the description in the claim that the particles were "liquid perfluorocarbon" was sufficient to denote that the particles themselves, which also have a coating of lipids, were indeed simply liquid perfluorocarbon. However, in order to clarify this, the description of the particles has been amended to read "lipid-coated particles consisting of liquid perfluorocarbon," thus clarifying that the particles themselves do not contain gas bubbles at the time imaging is done. No new matter has been added and entry of the amendment is respectfully requested.

The Rejection Under 35 U.S.C. § 102

Claims 20, 24 and 28, all independent claims, were rejected as assertedly anticipated by Unger, U.S. 5,922,304. Applicants respectfully submit that the clarifying amendment disposes of this rejection. It is clear from '304 that the particles described for use in imaging are "gas-filled microspheres." The only mention of including liquid fluorocarbons is in addition to the gas bubble that is created. Column 5, line 24, states that "optionally the contrast medium may *further* comprise a liquid fluorocarbon compound, *e.g.*, perfluorocarbon to further stabilize the microspheres." The purpose of the liquid portion is to stabilize the gas bubbles and not to provide imaging. Thus, it is clear that the microspheres of Unger cannot "consist of" liquid perfluorocarbon. Although this should be sufficient in and of itself to distinguish '304, applicants respectfully point out that the '304 particles do not in fact contain a targeting agent (*i.e.*, ligand). As is clear from the section pointed to by the Office, column 9, lines 65+, it is the size of the particles that is critical in targeting specific types of tissue, not any ligand. Indeed, applicants have searched the electronic version of '304, and the word "ligand" does not appear anywhere. Thus it is clear that '304 cannot anticipate the claims as amended. Applicants respectfully request this basis for rejection be withdrawn.

The Rejection Under 35 U.S.C. § 103

Claims 20-31, all claims pending, were rejected as assertedly obvious over Unger '304, and it appears that this has also been combined with Unger U.S. patent 5,585,112. The Office assumes in making this rejection that the only distinction between the description in '304 and the present invention is that the perfluorocarbon particles of the present invention contain a targeting ligand, such as an antibody, specifically, in their lipid coating whereas, as has been pointed out above, it is clear that the microspheres of '304 do not. Therefore, it appears that the '112 patent of Unger is cited because it describes the use of antibodies as targeting agents. The Office points to column 25, lines 15+. As will be argued below, the distinction between the presently claimed methods and those of Unger go far beyond the possible use of antibodies as targeting agents in the compositions of the present invention. However, applicants respectfully point out that the cited portion of '112 is taken out of context. It is clear from the context that the major targeting feature is provided by focusing the sound waves, not a targeting ligand. As stated, "Thus by focusing the sound waves on the selected tissue to be treated, the therapeutic will be released totally at the target tissue. As a further aid to targeting, antibodies, carbohydrates...." Thus, although alluding to the possibility of the use of such targeting ligands, it is something of a stretch to state that '112 actually teaches this.

Nevertheless, both of Unger's patents, '304 and '112 are clearly directed to the use of gas-filled microspheres as contrast agents. Indeed the titles of both patents as well as the abstracts indicate as much. There is no suggestion anywhere in either patent that a liquid perfluorocarbon could be substituted for the gas-filled microspheres. The documents clearly teach away from any other formulation. The importance of using a gas phase is emphasized, for example, in the '304 patent at column 7, line 14, which states "the stabilized gas filled microspheres of the present invention are believed to rely on this phase magnetic susceptibility

difference..." referring to the fact that gas, liquid and solid phases have different magnetic susceptibilities at column 7, lines 1-3. Thus, there is no suggestion whatsoever in either Unger patent to use anything other than gas-filled microspheres.

While the foregoing should be adequate to demonstrate that the claimed subject matter is not suggested by '304 or '112 either alone or in combination, applicants point out that the use of the claimed liquid perfluorocarbon particles of the invention has advantages over the gas-filled microspheres of Unger. For example, the invention microspheres can be sterilized by heat, whereas the gas-filled microspheres of Unger are problematic in that regard. Specifically, Unger in '112, column 16, lines 8-11, states that

> Once gaseous precursor filled liposomes are formed, they generally cannot be sterilized by heating at a temperature that would cause rupture. Therefore it is desirable to form the gaseous precursor filled liposomes from sterile ingredients and to perform as little subsequent manipulation as possible to avoid the danger of contamination.

The particles of the present invention on the other hand, can be sterlized intact prior to use by thermal means.

Further, it is noted in Unger '112 that in many cases filtration is necessary to obtain microspheres of uniform size and that the size obtained is dependent on process conditions. See column 15, lines 7-11. The particles of the present invention, on the other hand, can be produced directly over a broad range of conditions to obtain a narrow size distribution.

These features are important practical advantage. Applicants recognize that these features are not claim limitations, but they are significant inherent advantages of the particles used in the methods as claimed.

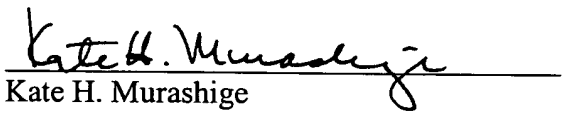
For these reasons, it is believed that the rejection over Unger '304 and '112 may properly be withdrawn.

CONCLUSION

The only outstanding rejections are over the art – Unger '304 and '112. Both of these documents are focused on gas-filled microspheres as contrast agents. Neither document alone nor the documents together suggest the use of particles which consist of liquid perfluorocarbons as their core, and do not contain any gas bubbles. There is no suggestion that anything other than gas bubbles is appropriate in these documents. Accordingly, applicants believe that claims 20-31 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 532512000312.

Respectfully submitted,

Dated: December 11, 2003 By: 

Kate H. Murashige
Registration No. 29,959

Morrison & Foerster LLP
3811 Valley Centre Drive,
Suite 500
San Diego, California 92130-2332
Telephone: (858) 720-5112
Facsimile: (858) 720-5125